

REPORTS

BIOCHEMICAL MEDIATORS OF IMMEDIATE TYPE HYPERSENSITIVITY

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The primary chemical mediators of immediate type hypersensitivity include histamine, the eosinophil chemotactic factor of anaphylaxis (ECF-A), slow reacting substance of anaphylaxis (SRS-A), and platelet activating factor (PAF). These mediators exist either preformed or are newly generated and subsequently released following activation of the target cell. The nature of these mediators, their interrelationships, the biochemical concomitants, and controls over their generation and release are the focus of this review.

All four primary mediators have been associated with the human peripheral blood basophil [1] and the human tissue mast cell [2-4]. Histamine and ECF-A exist preformed and are granule associated [4] while SRS-A and PAF must be generated prior to their release. These mediators may be generated and released following the interaction of antigen and specific IgE antibody bound to receptors on the surface of the mast cell or basophils, or following interaction of mast cells or basophils with antibody directed toward the IgE molecule itself. Upon the bridging of two or more IgE molecules upon the surface of the target cell, a series of biochemically separable steps ensues, resulting in the generation of unstored mediators and culminating in the release of both the generated and preformed mediators.

Temporally, the first step in the sequence thus far delineated is the activation of a proesterase to an active diisopropylfluorophosphate (DFP)-inhibitable serine esterase. This enzyme, in the presence of calcium ions appears to have autocatalytic properties [5]. Following the DFP-sensitive step is an energy-dependent, 2-deoxyglucose-inhibitable step and finally a divalent cation, EDTA-inhibita-

ble reaction [5]. The nucleotides cyclic adenosine monophosphate (cAMP) and cyclic guanosine phosphate (cGMP) in concert with these biochemical processes manifest another level of control and act to modulate the release of mediators from target tissues. Beta adrenergic stimulation, interaction with cholera toxin, prostaglandins of the E series or methyl xanthines lead to the accumulation of cAMP and decreased mediator release [6], while alpha adrenergic stimuli, or interaction with small amounts of prostaglandins of the F series, lead to decreases in cAMP and augmentation of mediator release [7]. Moreover, the exogenous addition of analogues of cGMP or cholerergic stimuli which presumably act to elevate intracellular concentrations of cGMP also augment mediator release [6]. The exact step or steps in the reaction sequence of generation and release of mediators modulated by the cyclic nucleotides is unclear and may include both control over the generation of mediators as well as release, perhaps via alterations in the alignment of microtubules and microfilaments.

An understanding of the chemical and functional nature of the specific factors released provides the basis for an approach to unravelling the mechanisms underlying pathobiologic alterations manifest by disease states. The preformed mediator histamine is formed from L-histidine and inactivated by oxidative deamination with or without methylation [8]. In vivo histamine is known to alter venular permeability and to stimulate the respiratory irritant receptor [9] and to constrict bronchial smooth muscle.

ECF-A is also preformed [4] and is an acidic, approximately 400 mw tetrapeptide [10] of limited heterogeneity. ECF-A preferentially attracts and chemotactically deactivates eosinophils [11]. It is susceptible to pronase and subtilin digestion but resists trypsin or chymotrypsin degradation [12]. ECF-A preferentially attracts eosinophils and is the most potent eosinophilotactic factor when compared to active site or complement derived chemotactic factors [13]. Following interaction with ECF-A, eosinophils reveal diminished responsiveness to subsequent chemotactic stimulation, termed deactivation, a phenomenon presumed to allow attracted eosinophils to remain at a site and exert a regulatory function.

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Abbreviations:

cAMP: cyclic adenosine monophosphate
cGMP: cyclic guanosine monophosphate
DFP: diisopropylfluorophosphate
ECF-A: eosinophil chemotactic factor of anaphylaxis
EDTA: ethylenediamine tetraacetic acid
PAF: platelet activating factor
SRS-A: slow reacting substance of anaphylaxis

SRS-A is an acidic sulfur containing 300 mw lipid [14] inactivated by limpet [15] or human eosinophil [11] arylsulfatase. SRS-A can be found immediately prior to release in tissues following activation [16]. SRS-A has been presumed to originate in mast cells or basophils based upon its generation by IgE dependent reaction in human mast cell-rich tissues [3,17], peripheral blood leukocytes [18], or ionophore activation of leukemic basophils [1]. SRS-A can be appreciated intracellularly following levels of activation below threshold for histamine release [16], and following greater degrees of challenge, release proceeds beyond the time of plateau for histamine or ECF-A release [16]. Furthermore, the release of SRS-A can be augmented markedly by the addition of cysteine to the reaction medium [19]. SRS-A may also be generated in rodent tissues by an IgG_a, neutrophil, and complement-dependent mechanism [20]. SRS-A in vivo contracts smooth muscle, enhances vascular permeability [21], and decreases pulmonary compliance [22].

PAF, defined by its ability to mediate serotonin release from platelets, has been appreciated following IgE-dependent reactions in human lung [23] and peripheral blood leukocyte suspensions [24] and by calcium ionophore activation of human leukemic basophils. PAF generated by an IgG_a-dependent reaction in the rat peritoneal cavity has an mw of 300 and is stable to arylsulfatase but sensitive to eosinophil phospholipase D enzymatic degradation [25]. The exact-functional properties of this factor in vivo are unknown.

The possible functional interrelationships of these chemical mediators are mainly speculative. It is known that histamine and SRS-A potentiate one another in bronchial smooth muscle strips [26] and may act synergistically in vascular smooth muscle as well. It is also possible that these primary mediators may induce the production of such secondary mediators as prostaglandins or kinins. Finally, it should be noted that the potential for destruction of three of these primary mediators is inherent in the properties of the fourth. That is, ECF-A, by attracting eosinophils, attracts and localizes to the site of mediator release

a cell which contains histaminase to inactivate histamine [27], arylsulfatase B to inactivate SRS-A [15], and phospholipase D to inactivate PAF [28].

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